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FORM PTO-1595 (Modified) (Rev. 03-01) OMB No. 0651-0027 (exp. 5/31/2002) POBAREV03		Docket No.: BN 35 B SHEET <input type="checkbox"/> U.S. DEPARTMENT OF COMMERCE <input checked="" type="checkbox"/> Y Patent and Trademark Office	
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1. Name of conveying party(ies): 1. Paul CHAPLIN 2. Paul HOWLEY 3. Christine MEISINGER		2. Name and address of receiving party(ies): Name: <u>BAVARIAN NORDIC A/S</u> Address: <u>Ved Amagerbanen 23</u>	
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3. Nature of conveyance: <input checked="" type="checkbox"/> Assignment <input type="checkbox"/> Merger <input type="checkbox"/> Security Agreement <input type="checkbox"/> Change of Name <input type="checkbox"/> Other _____		City: <u>Copenhagen S</u> State/Prov: <u></u> Country: <u>DENMARK</u> ZIP: <u>DK-2500</u>	
Execution Date: <u>April 14, 2003</u>		Additional name(s) & address(es) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
4. Application number(s) or patent numbers(s): If this document is being filed together with a new application, the execution date of the application is:			
Patent Application No. <u>10/439,953</u>		Filing date <u>May 16, 2003</u>	
		B. Patent No.(s)	
		OPR/Finance	
Additional numbers _____		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
5. Name and address of party to whom correspondence concerning document should be mailed: Name: <u>G. PATRICK SAGE</u> Registration No. <u>37 710</u> Address: <u>500 COLUMBIA PLAZA</u> <u>350 EAST MICHIGAN AVENUE</u>		6. Total number of applications and patents involved: <input type="checkbox"/> 1	
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PATENT
REEL: 014354 FRAME: 0149

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Title of the Invention MODIFIED VACCINIA ANKARA VIRUS VARIANT.																										
Inventors (assignors) <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Name</th> <th style="width: 50%;">Address</th> </tr> </thead> <tbody> <tr> <td>Paul CHAPLIN</td> <td>Wohlerstrasse 22, 81247 Munchen, Germany</td> </tr> <tr> <td>Paul HOWLEY</td> <td>Kopernikusweg 9, 82162 Martinsried, Germany</td> </tr> <tr> <td>Christine MEISINGER</td> <td>Kirchenstrasse 9, 82194 Gröbenzell, Germany</td> </tr> <tr> <td></td> <td>60 Rose Avenue, Glen Waverly, Vic 3150, Australia</td> </tr> <tr> <td></td> <td></td> </tr> </tbody> </table>			Name	Address	Paul CHAPLIN	Wohlerstrasse 22, 81247 Munchen, Germany	Paul HOWLEY	Kopernikusweg 9, 82162 Martinsried, Germany	Christine MEISINGER	Kirchenstrasse 9, 82194 Gröbenzell, Germany		60 Rose Avenue, Glen Waverly, Vic 3150, Australia														
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Assignee <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Name</th> <th style="width: 50%;">Address</th> </tr> </thead> <tbody> <tr> <td>BAVARIAN NORDIC A/S</td> <td>Ved Amagerbanen, DK-2500 Copenhagen S, Denmark</td> </tr> </tbody> </table>			Name	Address	BAVARIAN NORDIC A/S	Ved Amagerbanen, DK-2500 Copenhagen S, Denmark																				
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PATENT
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EXHIBIT 3

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July 19, 2005

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
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U.S. PATENT: 6,913,752

ISSUE DATE: July 05, 2005

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M. K. HAWKINS

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(12) United States Patent
Chaplin et al.

(10) Patent No.: US 6,913,752 B2
(45) Date of Patent: Jul. 5, 2005

(54) MODIFIED VACCINIA ANKARA VIRUS VARIANT

(75) Inventors: Paul Chaplin, Munich (DE); Paul Howley, Martinsried (DE); Christine Meisinger, Grobenzell (DE)

(73) Assignee: Bavarian Nordic A/S, Copenhagen S (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 56 days.

(21) Appl. No.: 10/439,439

(22) Filed: May 16, 2003

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(52) U.S. Cl. 424/199.1; 424/232.1; 424/208.1; 424/281.1; 435/235.1; 435/236; 435/320.1

(58) Field of Search 435/235.1, 236, 435/237, 320.1; 424/199.1, 208.1, 232.1, 278.1, 281.1, 93.2, 93.6; 536/23.72; 514/44

(56) References Cited

U.S. PATENT DOCUMENTS

5,155,020 A * 10/1992 Paoletti 435/69.1
5,185,146 A 2/1993 Altenburger
5,494,807 A * 2/1996 Paoletti et al. 435/69.3
5,789,245 A 8/1998 Chang et al.

FOREIGN PATENT DOCUMENTS

WO	WO9702355 A	2/1997
WO	WO 98/56919	12/1998
WO	WO 00 28016	5/2000
WO	WO 01 68820	9/2001
WO	WO 02/24224	3/2002

OTHER PUBLICATIONS

Eo et al, The Journal of Immunology 166:5473-5479, May 2001.*
Holzer et al (Journal of Virology 73:4536-4542, 1999).*
Antoine et al (Virology 244:365-96, 1998).*
Gilbert et al (Biol. Chem. 380:299-303, 1999).*

Moss et al. "Host range restricted, non-replicating vaccinia virus vectors as vaccine candidates." Advances in Experimental Medicine and Biology 397:7-13, 1996.*

Wyatt et al (PNAS 101:4590-4595, 2004).*

Earl et al (Nature 428:182-185, 2004).*

Stittelaar et al. Vaccine 19:3700-3709, 2001.*

Behera AK, Kumar M, Lockey RF and Mohapatra SS (2002) Hum. Gene Ther. Sep. 20; 13(14):1697-709.

Belyakov IM, Earl P, Dzutsev A, Kuznetsov VA, Lemon M, Wyatt LS, Snyder JT, Ahlers JD, Franchini G, Moss B and Berzofsky JA. (2003) Proc. Natl. Acad. Sci. 100:9458-9463. Hanke T, Samuel RV, Blanchard TJ, Neumann VC, Allen TM, Boyson JE, Sharpe SA, Cook N, Smith GL, Watkins DL, Cranage MP and McMichael AJ (1999) Journal of Virology 73:7524-7532.

Schneider J, Gilbert SC, Blanchard TJ, Hanke T, Robson KJ, Hannan CM, Becker M, Sinden R, Smith GL and Hill AVS. (1998) Nature Medicine 4:397-402.

Mayr, A., Zbl Vet B 23, 417-430 (1976).

Blanchard, J.T., et al., Journal of General Virology, 79, 1159-1167 (1998).

Caroll, W.M. and Moss, B., Virology 238, 198-211 (1997).

Meyer, H., et al., Journal of general virology, 72, 1031-1038 (1991).

Bender, et al., Journal of Virology, vol. 70, No. 9, pp. 6418-6424 (Sep. 1, 1996).

Schneider, et al. (1998), Nature Medicine 4, 397-402.

Sutter, et al. (1994), Vaccine 12, 1032-1040.

Stittelaar, et al. Vaccine 19:3700-3709, 2001.

Sutter and Moss Proc. Natl. Acad. Sci. USA 89:10847-51, 1992.

Schieflinger, et al, Proc. Natl. Acad. Sci. USA 89:9977-81, 1992.

Merchliinsky, et al. Virology 190:522-6, 1992.

* cited by examiner

Primary Examiner—Mary E. Mosher

(74) Attorney, Agent, or Firm—The Firm of Huesschen and Sage

(57) ABSTRACT

The present invention provides an attenuated virus, which is derived from Modified Vaccinia Ankara virus and characterized by the loss of its capability to reproducitively replicate in human cell lines. It further describes recombinant viruses derived from this virus and the use of the virus, or its recombinants, as a medicament or vaccine. A method is provided for inducing an immune response in individuals who may be immune-compromised, receiving antiviral therapy, or have a pre-existing immunity to the vaccine virus. In addition, a method is provided for the administration of a therapeutically effective amount of the virus, or its recombinants, in a vaccinia virus prime/vaccinia virus boost inoculation regimen.

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Fig. 1A

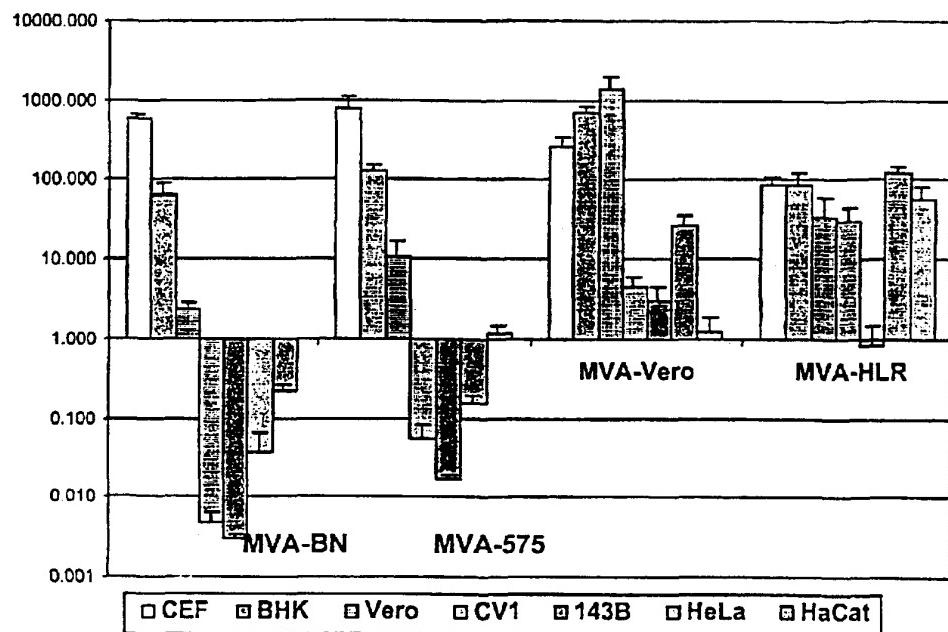
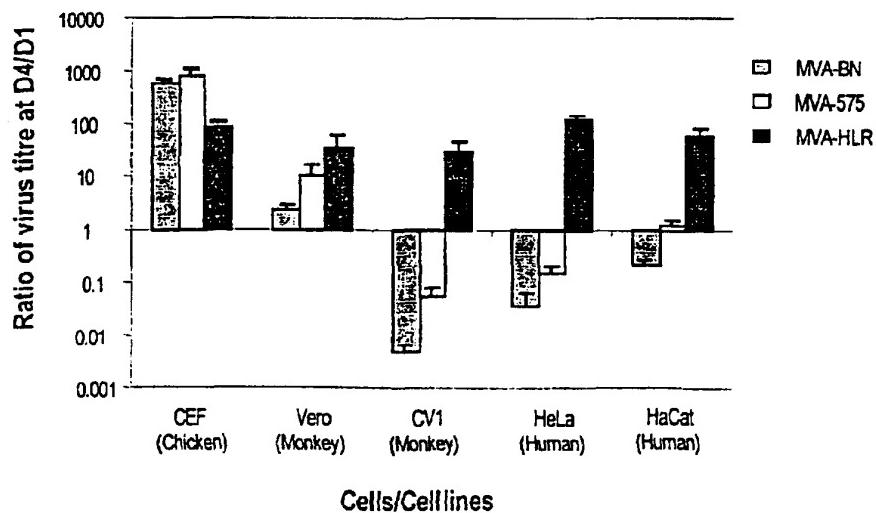
Ratio Output/Input
moi 0,05 day 4 post infection

Fig. 1B



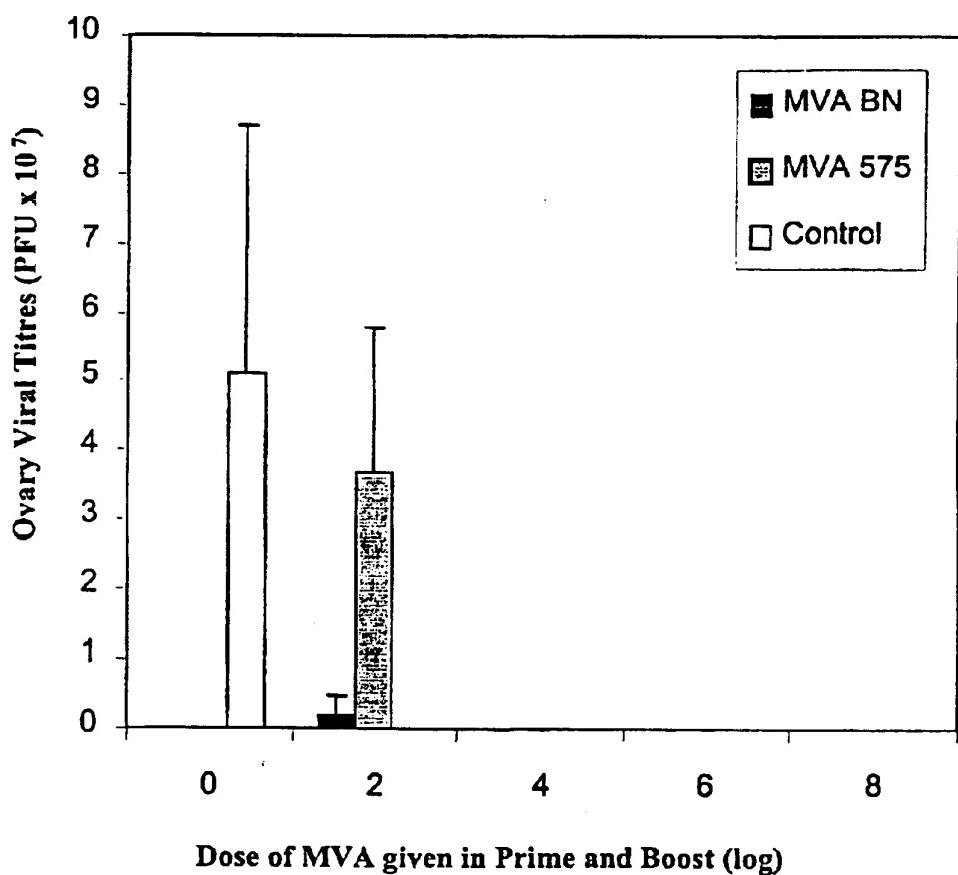
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Fig. 2



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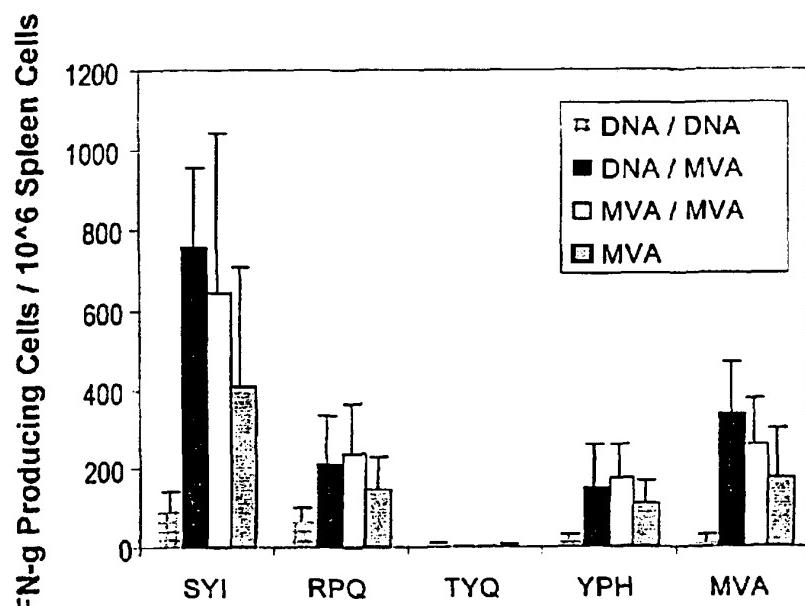
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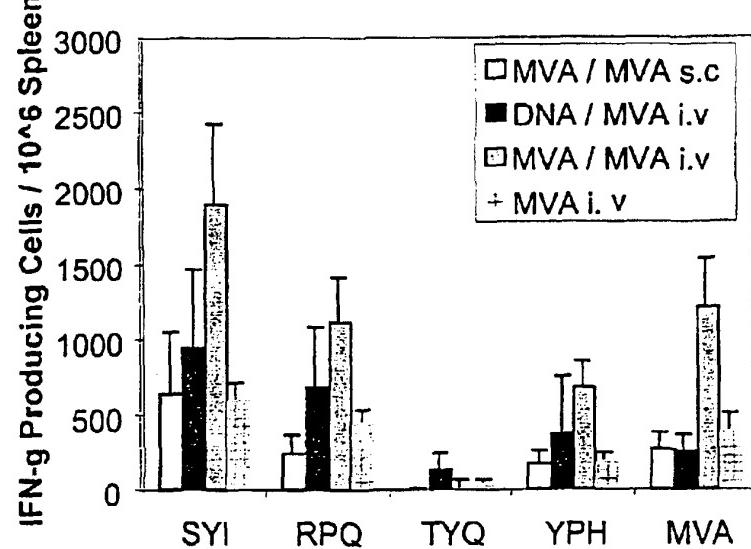
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Fig. 3

A



B



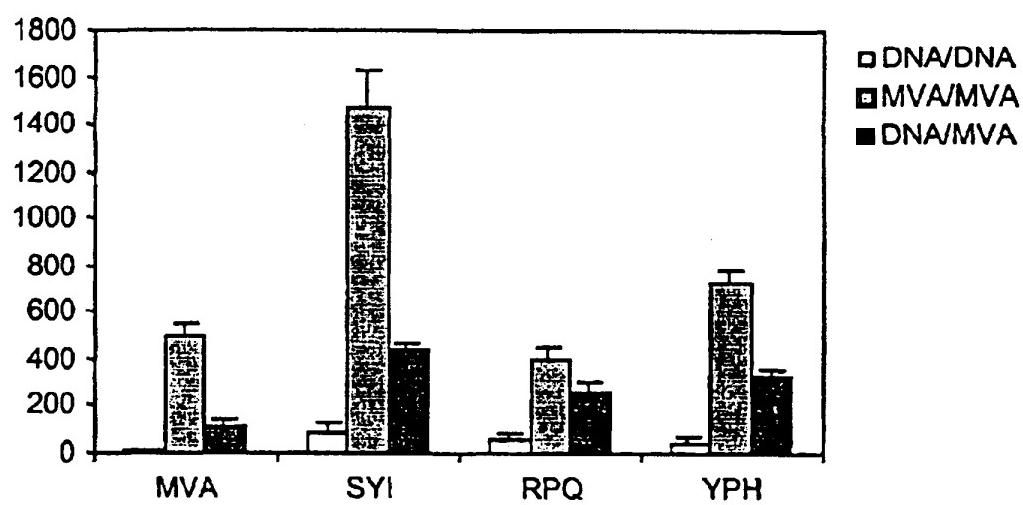
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Fig. 3C



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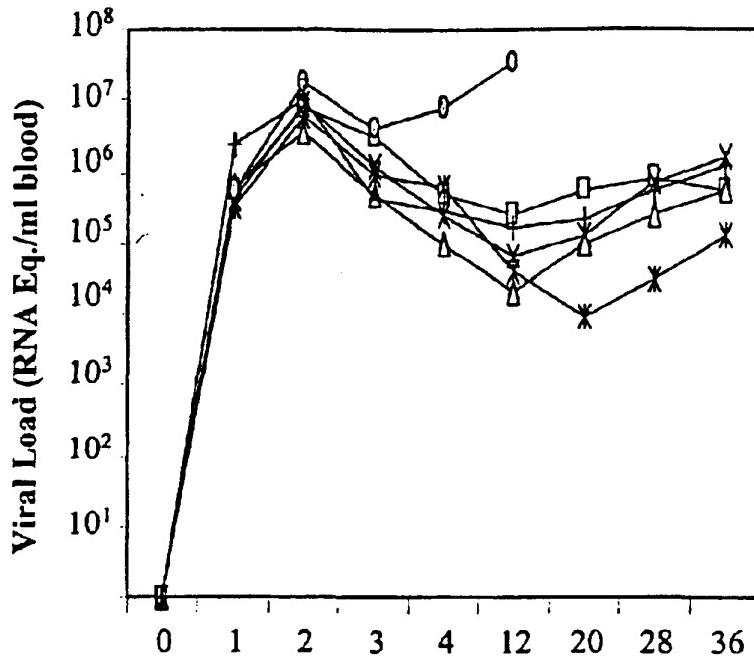
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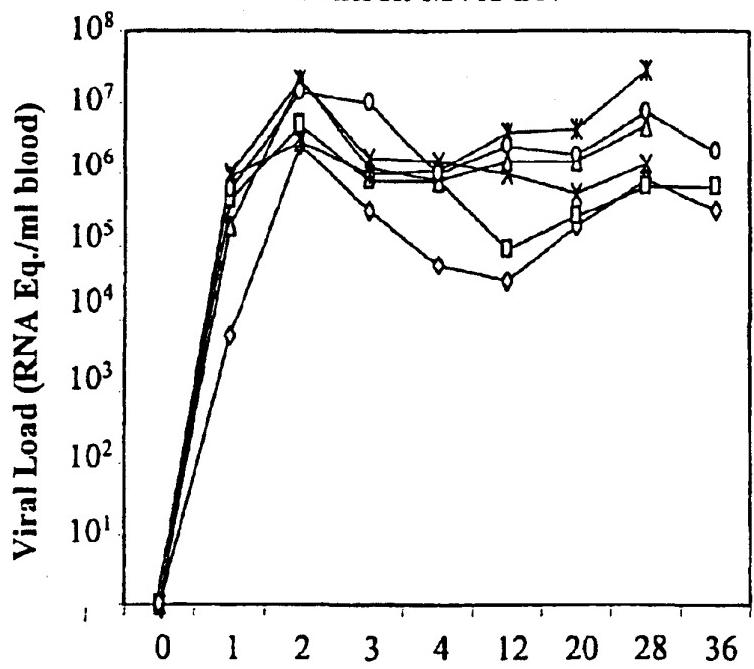
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Fig. 4

MVA nef vaccinated



Control: MVA-BN



Weeks Post Infection

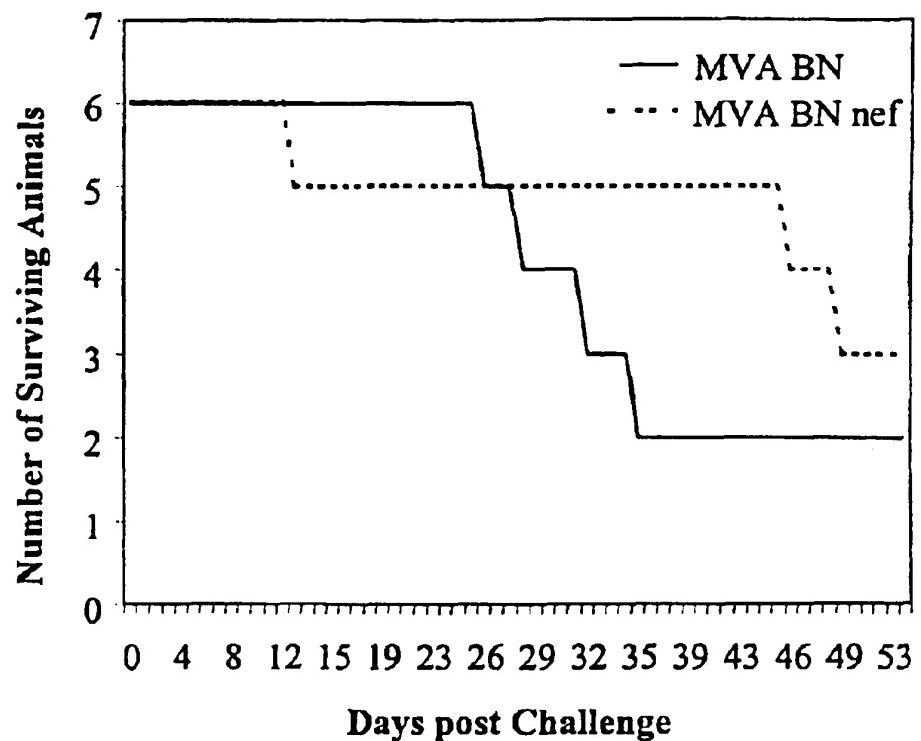
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Fig. 5



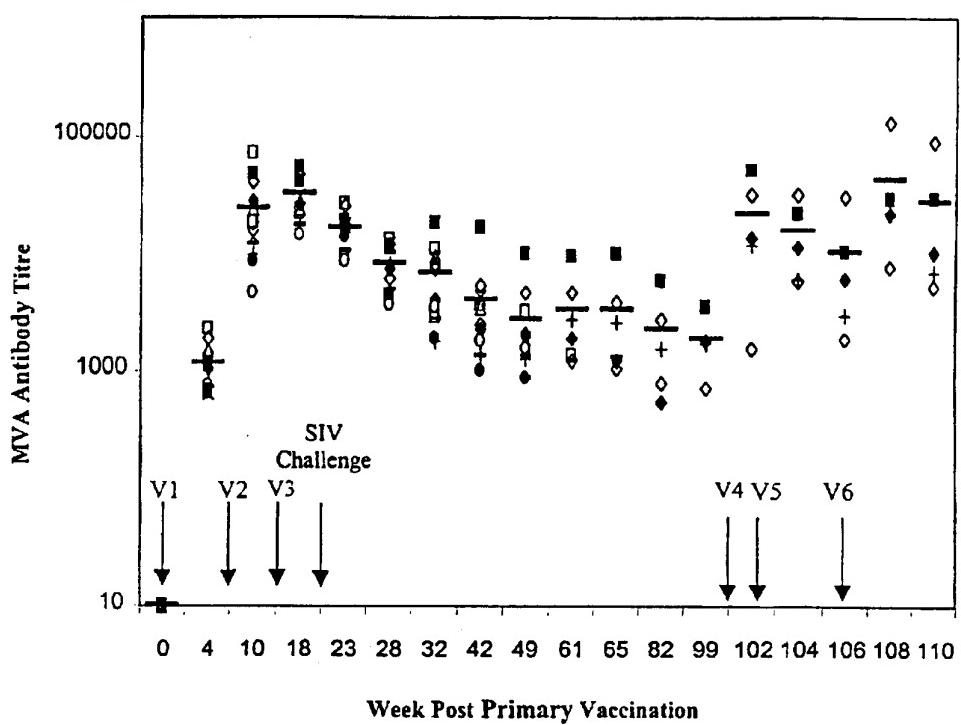
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Fig. 6



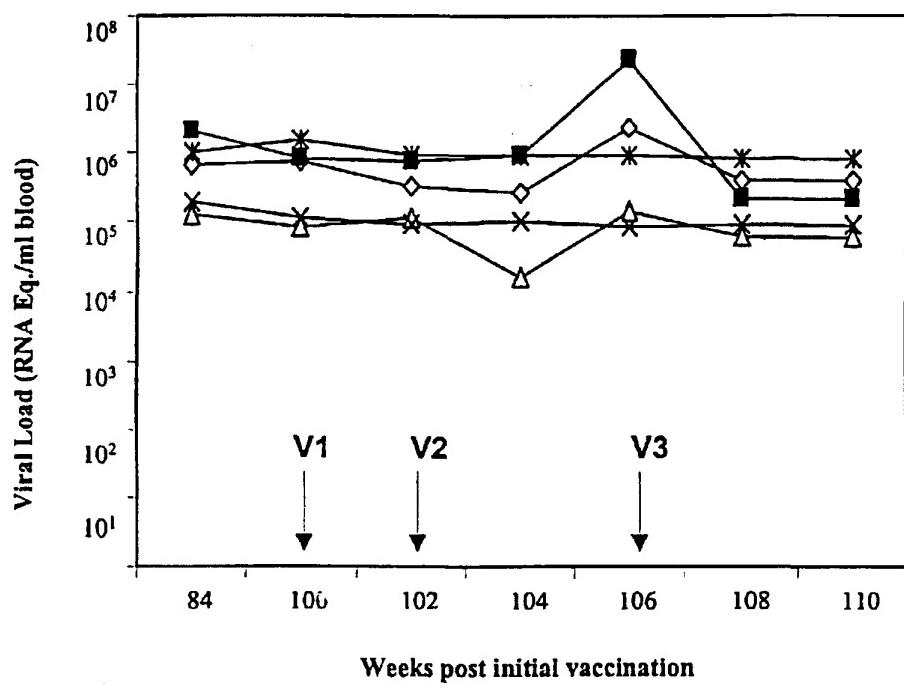
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Fig. 7



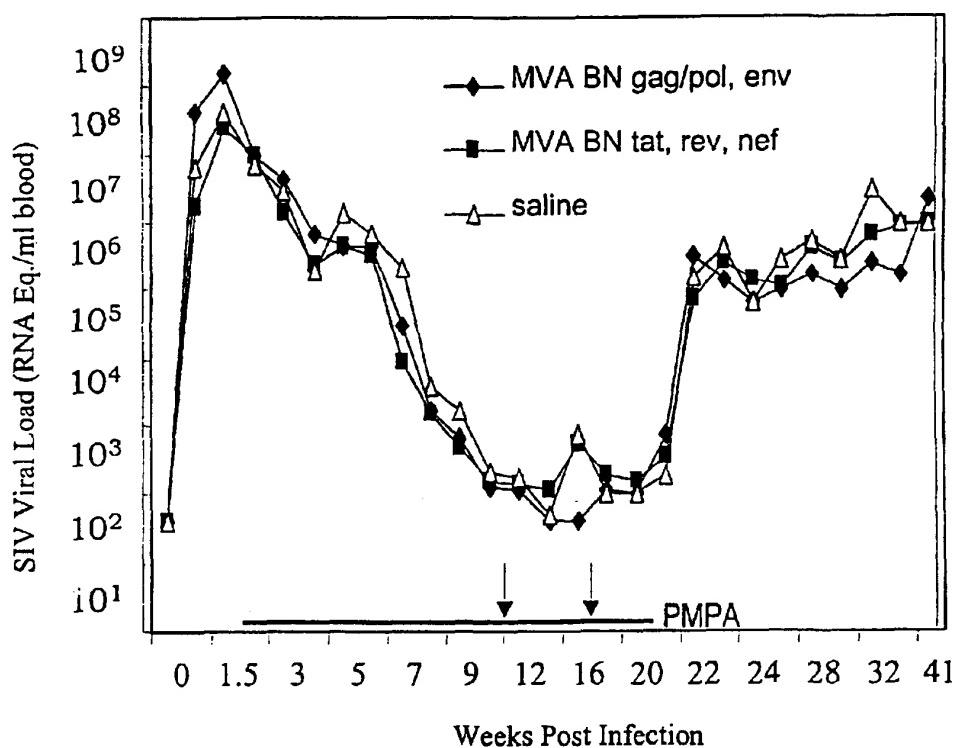
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Fig. 8

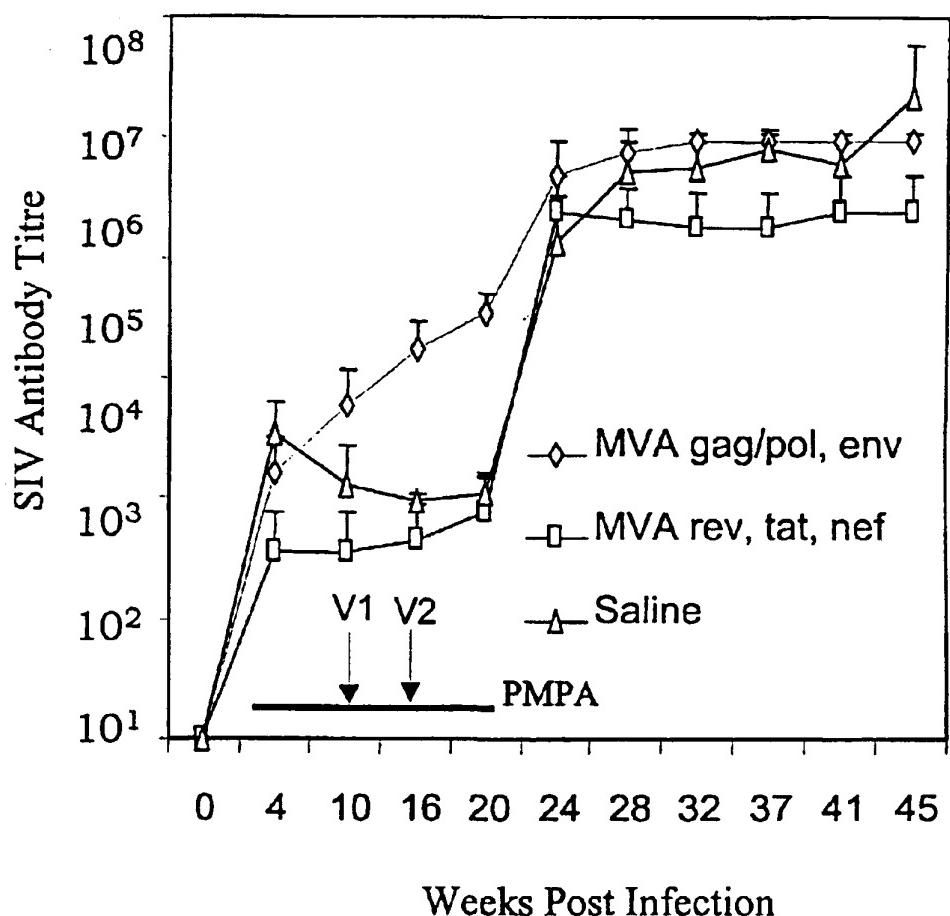


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Fig. 9

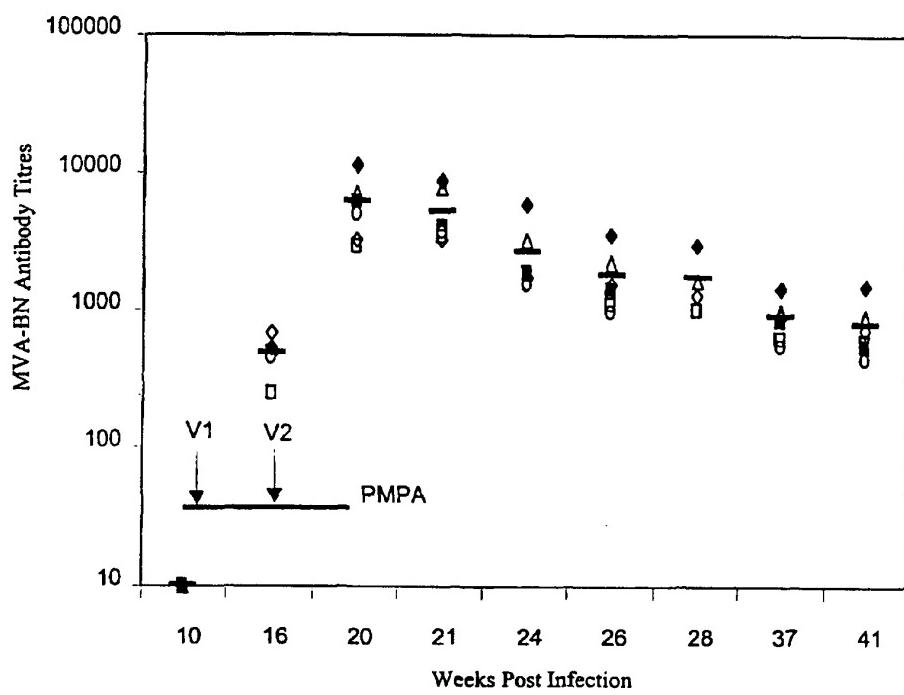
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Fig. 10



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Fig. 11

